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Body Composition and Bone Metabolism in Young Gaucher Disease Type I Patients Treated with Imiglucerase

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Abstract
Bone involvement is one of the most disabling complications in patients with type 1 Gaucher disease (GDI) and its pathophysiology is yet to be fully understood. It is well known that body composition is a determinant of bone mass. Previous reports indicating disturbance in glucose and lipid metabolism in GDI patients suggested a posible alteration in body composition in this group of patients.
Objective: To analyze body composition, bone mass and turnover in young adults with GDI receiving enzyme replacement therapy (ERT).
Population: 5 women and 4 men with GDI aged (X ± SD) 26.9 ± 6.9 years, receiving imiglucerase in a mean dose of 53 ± 13 IU/kg/2weeks, during 4.9 ± 3.9 years; and 145 sex and age matched healthy adults agreed to participate in the study. All control subjects had a body mass index (BMI) between 20 and 25 kg/m².
Methods: Total body dual X-ray absorptiometry (DXA) was used to measure body composition and bone mass. Serum creatinine, calcium, osteocalcin (BGP), and type I collagen beta carboxy-terminal telopeptide (βCTX) were determined in patients and controls. In addition, 25 hydroxyvitamin D (25OHD), and chitotriosidase activity were measured in patients.
Results: GDI patients presented statistically significant ($p<0.01$) lower BMI, bone mineral density (BMD), bone mineral content (BMC), lean mass (LM), and fat mass (FM), compared to controls. LM correlated positively with BMC and BMD in both groups ($p<0.01$). GDI patients receiving the lower dose of ERT (<60 IU/kg/2weeks) presented lower BMD values than those receiving the higher dose (≥60 IU/kg/2weeks) (0.968 ± 0.032 vs 1.088 ± 0.061 g/m², respectively, $p<0.001$). Mean BGP levels were similar in patients and controls, whereas βCTX levels were higher in GDI patients ($p<0.02$). All patients presented deficiency levels (<30ng/ml) of 25OHD.
Conclusions: Although the patients had been receiving ERT, they presented a significant diminution in all body composition parameters, the decrease was more evident in those receiving the lower dose. The reduction in bone mass was associated with an imbalance in bone turnover (increased bone resorption). The correlation between LM and bone mass, suggests that metabolic disturbance occurring in GDI patients may be indirectly responsible for bone mass reduction in GDI patients, by altering body composition.

Key words: Gaucher disease, bone turnover markers, bone mineral density, imiglucerase, body composition, DXA.
Abbreviations: Type I Gaucher disease (GDI), lean mass (LM), fat mass (FM), bone mineral density (BMD), bone mineral content (BMC), enzyme replacement therapy (ERT), osteocalcin (BGP), type I collagen beta carboxy-terminal telopeptide (βCTX), body mass index (BMI)

Introduction

Gaucher disease is the most common lysosomal storage disorder (Meikle et al. 1999). It is the result of genetic mutations, which cause a deficiency in the level of activity of lysosomal enzyme b-glucocerebrosidase (acid β-glucosidase) leading to the accumulation of glucosylceramide within the monocytes and macrophages of various organ systems. The affected organs include the spleen, liver, lung, kidneys, bone and bone marrow (Koprivica et al. 2000). Three basic clinical forms have been differentiated according to the degree of neurological involvement. The nonneuronopathic form, or type I Gaucher disease (GDI), is the most common form. The remaining forms are the acutely neuronopathic form (type II) and the subacutely neuronopathic form (type III) (Koprivica et al. 2000). The choice treatment for this disease is enzyme replacement therapy (ERT) with β-glucocerebrosidase, derived from human placenta (alglucerase) or from recombined DNA production (imiglucerase) (Cohen et al. 1998; Fiore et al. 2002).

Eighty percent of patients with GDI present skeletal involvement (bone crises, nonspecific bone pain, bone marrow infiltration, osteopenia, pathologic fractures, impairment of remodeling, osteoesclerosis and/or osteonecrosis), all of which are disabling complications with a negative impact on the patient's quality of life (Stowens et al. 1985; Wenstrup et al. 2002). Three different pathological processes are known to con-

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tribute to the skeletal manifestations in patients with GDI: 1) focal disease (osteonecrosis and osteosclerosis); 2) local disease (cortical thinning and long bone deformity) and 3) generalized osteopenia (resulting from abnormally high rates of bone resorption and reduced rates of bone formation) (Wenstrup et al. 2002). The clinical course of Gaucher disease varies greatly among individual patients and bone involvement is perhaps the most variable manifestation of the disease. Previous studies disclosed uniformly a significant reduction in bone mass in GDI child and adult patients (Fiore et al. 2002; Rosenthal et al. 1995; Pastores et al. 1996; Bembi et al. 2002; Ciana et al. 2003). The beneficial effect of ERT on bone mineral density (BMD) has been demonstrated only in long-term follow-up studies (4.5 years or more) (Lebel et al. 2004; Ciana et al 2005; Wenstrup et al. 2007). Studies assessing biochemical markers of bone turnover, a helpful tool to study skeletal metabolism, have shown controversial results, reporting decreased, normal or increased bone markers, both in patients with and without ERT (Fiore et al. 2002; Drugan et al. 2002; Schiffman et al. 2002; Ciana et al. 2003; Ciana et al. 2005).

There are reports indicating that patients with Gaucher disease present metabolic disturbance evidenced by alterations in their serum lipid profile (Cenarro et al. 1999; Alfonso et al. 2003), increased glucose production, and increased resting energy expenditure (REE) (Corrsmit et al. 1995; Holak et al. 1997). Therefore, body composition might be affected. Many studies have demonstrated that parameters of body composition (i.e. lean mass and fat mass) influence bone mass (Reid et al. 1992; Michaelsson et al. 1996; Sundeep et al. 1996; Baumgartner et al. 1996; Proctor et al. 2000; Pluijm et al. 2001; Matsuo et al. 2003; Lim et al. 2004; Makovey et al. 2005; Walsh et al. 2006). To our knowledge there are no reports evaluating body composition of GDI patients by means of dual X-ray absorptiometry (DXA).

Based on the above, the aim of this cross-sectional study was to analyze body composition, bone mass and bone turnover in young adult GDI patients receiving ERT.

Material and Methods

Patients

Nine young adult patients with GDI, 5 females (aged 22 to 27 years) and 4 males (aged 21 to 43 years), were studied. Diagnosis was confirmed by the presence of low acid b-glucosidase activity in leucocytes and the absence of disease involving the central nervous system. Mean age of patients was 26.9 ± 6.9 years (X ± SD) and their body mass index was 19.9 ± 1.8 kg/m^2 (range: 17-24 kg/m^2). All patients had been receiving ERT (imiglucerase) in a mean dose of 53 ± 13 IU/kg/2weeks (range: 30-71 IU/kg/2weeks) for 4.9 ± 3.9 years (range: 1.3-11.7 years). The mean total accumulated dose of ERT was 6.434 ± 5.501 IU/kg (range: 1.476-15.600 IU/kg). The patients had never received medication known to affect bone homeostasis (i.e., oral corticosteroids, fluoride, calcitonin, or bisphosphonates).

Controls

Ninety-four sex and age matched healthy adults, 34 females aged 24.4 ± 2.5 years (range: 20-29 years), and 60 males aged 32.7 ± 8.4 years (range: 21-49 years), agreed to participate in the study as controls for bone markers.

Fifty-one sex and age matched healthy adults, 11 females aged 25.1 ± 2.2 years (range: 21-28 years), and 40 males aged 33.2 ± 9.8 years (range: 20-49 years), agreed to participate in the study as controls for bone mass and body composition assessment. All control subjects presented body mass index (BMI) values between 20 and 25 kg/m^2.

None of the control subjects had a history of disease or had taken drugs known to affect bone metabolism.

The protocol was approved by the Ethics Committee of the Hospital de Clínicas, and written informed consent was given by both patients and controls.

Clinical Evaluation

A questionnaire including personal data, history of splenectomy, and history of bone involvement (bone pain and crises, pathological fractures, and osteonecrosis) was answered by patients. The presence of hepatomegaly was evaluated qualitatively using different available methods (ultrasound, computed tomography or physical examination). Anthropometric meassurements were performed in patients and controls using standard techniques.

Bone Mass and Body Composition

Total body bone mineral density (BMD), bone mineral content (BMC), fat mass (FM) and lean mass (LM) were measured using DXA (Lunar DPX). Technical details, coefficients of variation (CV) and normal values are reported elsewhere (Vega et al. 1993; Oliveri et al. 1999; Wittich et al. 2001).

Laboratory Tests

Overnight fasting blood samples were taken before 10 am. The following serum laboratory tests were performed in GDI patients: calcium (sCa) (reference value (RV): 8.9-10.4 mg/dl), creatinine (sCr) (RV: 0.5-1.4 mg/dl), 25 hydroxyvitamin D (25OHD) (desirable level: over 30 ng/ml), (Dawson-Hughes et al. 2005), and chitotriosidase activity (Ch-Pl) (RV: 0.05-1.00 mmol/min/ml). Serum osteocalcin (BGP) (RV: 11-46 ng/ml) was measured as a marker of bone formation, whereas serum type I collagen beta carboxy-terminal telopeptide (βCTX) was assessed as a marker of bone resorption, in patients and controls. sCr and sCa, were determined following standard methods (Zeni et al. 2001). Levels of 25OHD were assessed using the I^{125} radioimmunometric method (RIE) (Diasorin Inc., Minnesota, USA). βCTX and BGP levels were determined employing Electrochemoluminescence (Elecsys Roche Diagnostics Penzberg, Germany). Activity of Ch-Pl was assessed in 8 of the 9 patients by means of a fluorometric method.

STATISTICS

All studied variables are presented as mean ± standard deviation. Statistical analyses were performed using SPSS 11.0 for Windows. Mann-Whitney test was used to compare values corresponding to patients and controls, and to compare patients according to the current dose of ERT (≥60 IU/kg/2weeks vs <60 IU/kg/2weeks). Rho Spearman correlations were calculated to analyze relationships among laboratory values, bone mass, body composition and ERT. A value of $p<0.05$ was considered significant.

RESULTS

The clinical characteristics of GDI patients are described in Table 1.

Prior to ERT, history of unspecific bone pain was reported in all patients, bone crises in 5, bone fracture in 2, and osteonecrosis (avascular femoral necrosis) in 3. After initiating ERT, one patient suffered a bone crisis and one patient had a bone fracture; bone pain decreased in six patients, increased in one, and remained unchanged in the remaining two.

Table 1. Characteristics of young type 1 Gaucher disease patients treated with enzyme replacement therapy.

Patient	Sex	Age (years)	Weight (kg)	Height (m)	BMI (kg/m^2)	ERT			Splenectomy	Hepatomegaly
						Current Dose (IU/kg/2w)	Duration of treatment (years)	Total accumulated dose (IU/kg)		
1	M	32	61	1.61	24	60	1.3	1888	+	+
2	M	43	53	1.64	20	60	1.7	2400	-	-
3	M	21	52	1.62	20	60	11.7	15120	+	-
4	M	25	71	1.86	21	60	5.2	7440	-	-
5	F	23	54	1.60	21	60	10.9	15600	+	+
6	F	27	41	1.55	17	30	3.0	2160	+	-
7	F	25	45	1.53	19	71	3.0	5112	-	+
8	F	24	47	1.53	20	43	6.5	6708	-	+
9	F	22	49	1.63	18	41	1.5	1476	-	+

M: male, F: female, BMI: body mass index, ERT: enzyme replacement therapy (imiglucerase).

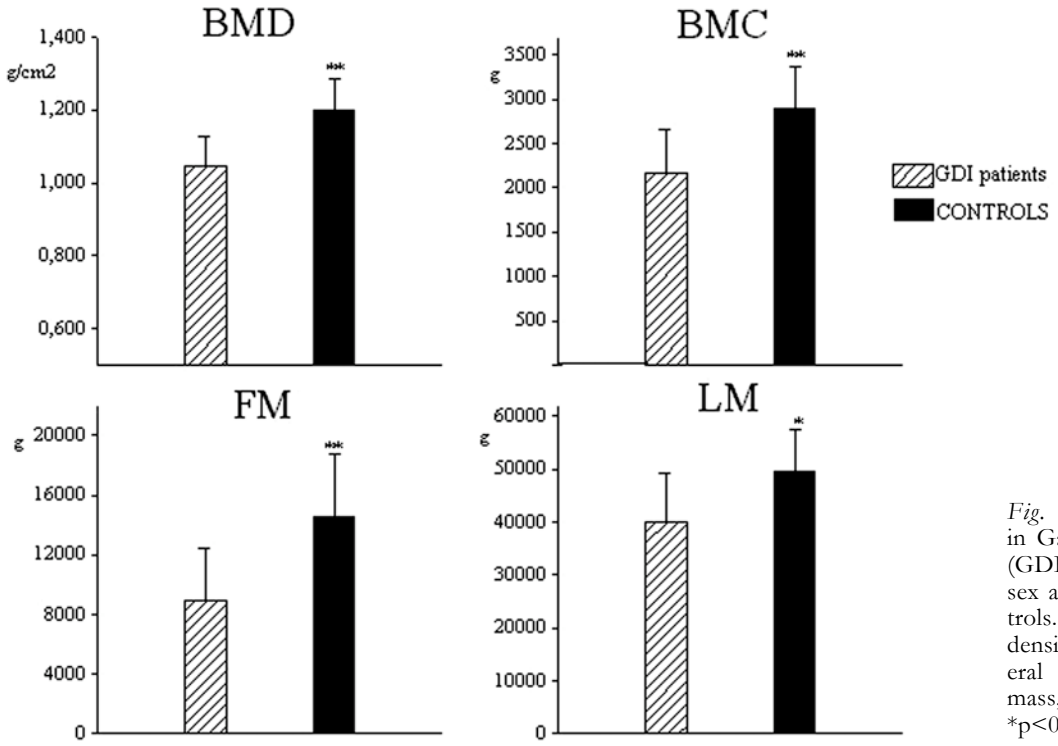

Fig. 1. Body composition in Gaucher disease type I (GDI) patients and healthy sex and age matched controls. BMD: bone mineral density, BMC: bone mineral content, LM: lean mass, FM: fat mass. *$p<0.01$, **$p<0.001$.

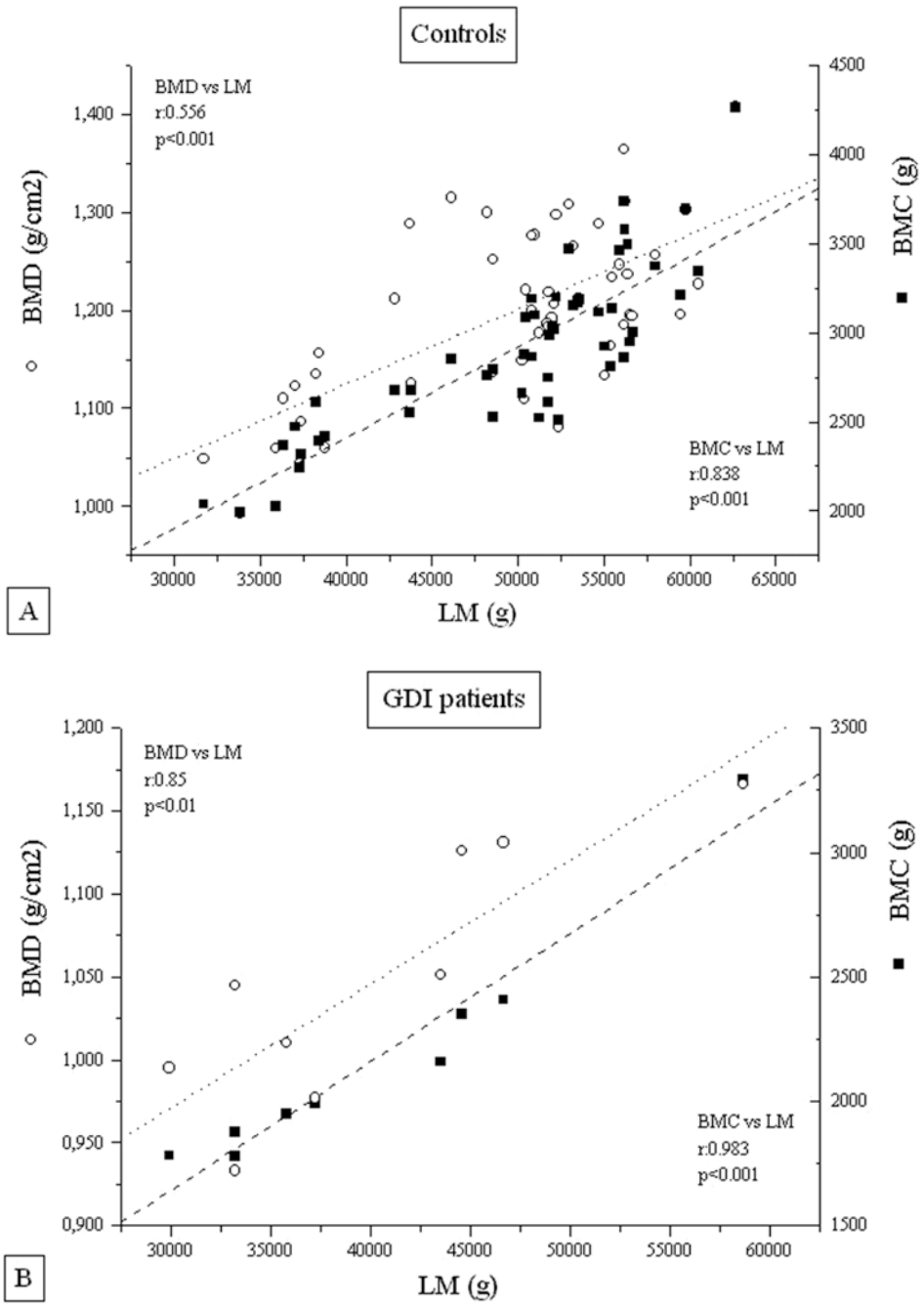

Fig. 2. Correlation between lean mass and bone mineral density -dotted lines- and between lean mass and bone mineral content –dashed lines-, A) in healthy sex and age matched controls; B) in Gaucher disease type I patients (GDI). LM: lean mass; BMD: bone mineral density; BMC: bone mineral content.

Bone mass and Body Composition

We observed that GDI patients had significantly lower BMI (19.9 ± 1.8 vs 22.9 ± 1.9 kg/m², p<0.001), BMD (1.048 ± 0.079 vs 1.199 ± 0.088 g/m², p<0.001), BMC (2175 ± 477 vs 2902 ± 465 g, p<0.001), LM (40293 ± 8977 vs 49685 ± 7741 g, p<0.01), and FM (8983 ± 3493 vs 14643 ± 4082 g, p<0.001) compared to controls (Fig. 1).

In both groups, GDI patients and controls, LM correlated significantly with bone mass parameters (Fig. 2). In contrast, FM did not correlate with bone mass in either the control or GDI group (data not shown).

Comparisons among patients, divided according to the current dose of imiglucerase (<60 vs ≥60 IU/kg/2 weeks), showed that BMD was ~11% lower in those receiving the lower dose (p<0.05). As regards body composition analysis, a decrease in BMC and LM (~21% and ~23%, respectively), and ~5.5% increase in FM was observed in individuals receiving the lower dose but the differences failed to reach statistical significance (Fig. 3).

Laboratory Tests

All patients had levels of sCr (0.64 ± 0.15 g/dl), and sCa (9.1 ± 0.4 mg/dl) within the normal reference values. However, mean sCr levels were lower in GDI patients compared to controls (0.85 ± 0.19 g/dl), p<0.01. High levels of Ch-P1 activity (103.5 ± 77.1 mmol/min/ml; range: 34.4-243.61 mmol/min/ml) were found in the 8 studied patients. Values of

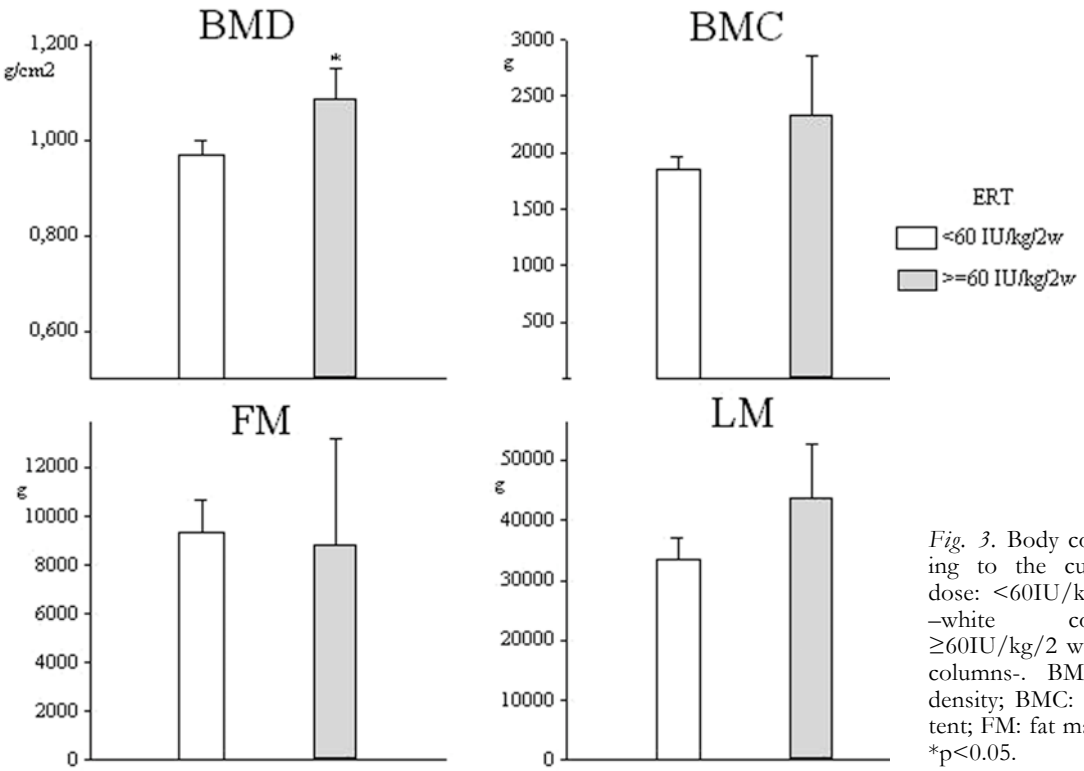

Fig. 3. Body composition according to the current imiglucerase dose: <60IU/kg/2weeks (n = 3) –white columns-, and ≥60IU/kg/2 weeks (n = 6) –grey columns-. BMD: bone mineral density; BMC: bone mineral content; FM: fat mass; LM: lean mass. *p<0.05.

25OHD (22.3 ± 3.0 ng/ml) were below the hypothetical desirable level of 30 ng/ml (Dawson-Hughes et al. 2005) in all patients.

Biochemical determinations of bone markers corresponding to patients and controls showed that βCTX was higher in GDI patients than controls (677 ± 293 vs 433 ± 180 ng/l, p<0.02), but BGP levels were similar in both groups (24.6 ± 13.7 vs 26.4 ± 9.8 ng/ml, ns). No correlation was found between the two bone turnover markers: βCTX and BGP.

Comparisons between patients, divided according to the current dose of imiglucerase (<60 vs ≥60 IU/kg/2weeks (n = 6)), showed that mean βCTX levels were similar in both groups (662 ± 395 vs 685 ± 274 ng/ml, respectively), and mean BGP levels were lower in patients receiving the lower dose (19.3 ± 7.5 vs 27.2 ± 15.9 ng/ml, respectively), though the difference failed to reach statistical significance.

A strong correlation was observed between both bone turnover marker levels, βCTX and BGP, and levels of Ch-P1 activity (r: 0.81, p<0.02 and r: 0.80, p<0.02; respectively).

No differences in bone mass, body composition or bone marker values were observed when comparing patients according to presence or absence of splenectomy, hepatomegaly, bone crises, bone pain and history of osteoporotic fractures.

Discussion

The GDI patients studied herein presented a decrease in bone mass, and significant changes in body composition (reduced BMD, BMC, FM and LM). It is known that the incidence of osteoporotic fractures is negatively related to BMD. Epidemiological studies indicate that the risk of osteoporotic fractures increases continuously as BMD declines, (Cummings et al. 1993), and it is well documented that body composition components influence bone mass (Michaelsson et al. 1996; Sundeep et al. 1996; Matsuo et al. 2003; Makovey et al. 2005; Walsh et al. 2006).

Correlations observed between LM and bone mass parameters suggest that the decrease in LM could be another determining factor of low bone mass in GDI patients.

Hypermetabolism was previously described in GDI patients, as evidenced by an increase in glucose production, and REE (Corssmit et al. 1995) (Hollak et al. 1997). In other diseases, such as hyperthyroidism, patients present an hypermetabolic state (Loeb 1996), and similar alterations in body composition (reduced BMC, BMD, FM, and LM; Gómez Acotto et al. 2002). It is noteworthy that specific treatment significantly reduced this hypermetabolic state in both pathologies, i.e. Gaucher disease and hyperthyroidism (Loeb 1996; Hollak et al. 1997; Alfonso et al. 2003). Body composition alterations can be reversed in patients attaining euthyroidism (Gómez Acotto et al. 2002), and it could indirectly explain why GDI patients treated with the higher dose of ERT were less affected. Analysis of the impact of ERT on body composition and bone mass showed that the decrease in bone mass and lean mass was less marked in patients receiving a higher monthly dose. In their study on 12 GDI adult patients (10 patients were receiving ERT), Fiore et al. (Fiore et al. 2002) observed severe osteopenia in both total skeleton and lumbar spine. The dose received by those patients ranged between 30 and 60 IU/kg/2w during 2-8 years; however, it must be pointed out that the data

were not presented according to dose or duration of treatment. Rosenthal's study on bone mass in a small group of patients by means of quantitative tomography showed that bone density improved after approximately 3 and a half years of ERT, suggesting that a longer treatment is necessary for skeletal alterations to improve compared with the length of treatment required for recovery of hematological alterations (Rosenthal el al. 1995). A recent study by Wenstrup performed in a large cohort of GD1 patients from the International Gaucher Registry (Wenstrup et al. 2007), showed that ERT with imiglucerase may increase lumbar spine BMD after long term treatment; however, not all their patients achieved normal BMD values (age- and sex-adjusted).

The results presented herein are in agreement with findings reported by Ciana et al., who found no relation between bone density at any site and GDI clinical dichotomous variables: splenectomy status, hepatomegaly status, history of osteoporotic fractures, osteonecrosis, or bone crises (Ciana et al. 2003). Conversely, Pastores et al. (Pastores et al. 1996) reported higher bone mass diminution in patients with splenectomy or hepatomegaly. It is possible that a relation cannot be established in the present study on account of the small study population.

The pathogenesis of bone changes in GDI is not fully understood and it is currently attributed to the combined effects of progressive marrow infiltration by the Gaucher cells, and macrophage enhancement of endothelial–mediated resorption. This is suggested by the evidence of local cytokine release in Gaucher cell cultures, as well as by the increase in serum levels of certain cytokines, such as interleukin-6 (IL-6), which stimulates bone resorption, and IL10, an inhibitor of osteoblastic activity (Gery et al. 1981; Balicki et al. 1995; Michelakakis et al. 1996; Allen et al. 1997; Allen et al. 1999).

Bone formation and bone resorption can be assessed non–invasively by measuring biochemical markers of bone turnover that can provide an insight into the pathogenesis of osteopenia /osteoporosis (Eastell et al. 1993; Valimaki et al. 1994). In the present study, alterations in bone turnover observed in GDI patients, in spite of ERT, could be attributed to an increase in resorption, since formation was similar to that of controls. BGP values did not differ from those of healthy sex and age-matched controls. Conversely, serum levels of βCTX, a marker of bone resorption, exhibited a significant increase in GDI patients, demonstrating an imbalance between both processes. The prevalence of resorption over formation may cause a continuous loss of bone mass, leading to osteopenia and osteoporosis. Several studies have confirmed a disturbance of the normal balance between bone formation and resorption in GDI patients. In agreement with the present study, Fiore et al. reported an increase in bone resorption markers, and normal bone formation markers in GDI patients without ERT (Fiore et al. 2002). However, Drugan et al. reported a reduction in bone turnover markers (BGP and βCTX) in 16 patients without ERT (Drugan et al. 2002). Finally, in a study performed on patients prior to initiating ERT treatment, Ciana et al. (Ciana et al. 2003) showed uncoupled bone remodeling that depended on the sensitivity of each marker.

Some histomorphometric studies of bone biopsies, a gold standard to evaluate changes in bone metabolism, performed in Gaucher patients without ERT, have shown an increase in bone resorption (Stowens et al. 1985; Ostlere et al. 1991).

The results obtained in the present group of GDI patients, using DXA, showed alterations in body composition parameters. To our knowledge, there are no previous reports evaluating body composition of GDI patients by means of DXA. The observed alterations may be the result of a hypermetabolic state, which may also be implicated in the physiopathology of osteopenia/osteoporosis in GDI patients.

In agreement with previous studies the group of GDI patients studied herein showed a significant decrease in bone mass associated to uncoupled bone turnover with high resorption, in spite of ERT.

The alteration in body composition parameters described in this study, mainly decreased lean mass, may also be implicated in the physiopathology of osteopenia/osteoporosis in GDI patients.

It is necessary to conduct further longitudinal studies on larger population in order to elucidate whether this uncoupling in bone remodeling and the alterations in body composition are determinants of the decrease in bone mass.

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